30 JUN 2009

Docket No.: 3493-0170PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Elie LEVERD et al.

Application No.: 10/584,445 Confirmation No.: 4148

Filed: June 22, 2006 Art Unit: 1614

For: PHARMACEUTICAL COPOSITION OF VINFLUNINE WHICH IS INTENDED FOR PARENTERAL ADMINISTRATION PREPARATION METHOD THEREOF AND USE OF SAME Examiner: T. P. Thomas

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madam:

I, Elie Leverd, do declare and say as follows:

1. I am one of the Inventors of the above-identified application. A copy of my Curriculum Vitae (five pages) is attached showing my qualifications and experience in the area of pharmaceutical formulations.

2. I have reviewed the most recent Office Action dated January 26, 2009 which issued by the US Patent and Trademark Office in connection with the above-identified application. I note that this Office Action includes rejections against the present patent claims based on the combination of two or more of the disclosures of: [1] GlaxoSmithKline ("Prescribing Information; Navelbine (vinorelbine tartrate) Injection", 2002, Nov., pp. 1-17); [2] Duflos '377 (US 6,127,377); [3] Wolgemuth '643 (CA 2,001,643) and [4] Howell ("Anti-vascular effects of

vinflunine...," *British Journal of Cancer* (2001) 84 (2), pp. 290-295.). I offer the following expert opinion relevant to the distinctions between the presently claimed and disclosed invention of the above-identified application and these references cited against the present application.

Evidence of Unexpected, Advantageous Properties of Present Invention

3. The disclosed and presently claimed invention is directed to a vinflunine pharmaceutical composition in the form of a stable and sterile aqueous solution of a water-soluble vinflunine salt at a pH between 3 and 4, which does not contain any sugar, sugar-based polyol or other preservatives, as recited in claim 1. As explained at pages 1-4 of the present specification, conventional pharmaceutical formulations containing vinflunine did not exhibit acceptable storage stability properties or required somewhat complex methods for preparing injectable formulations.

4. The improved stability properties exhibited by the composition of the present invention are evidenced by the test results described in connection with Examples 1 and 2 at pages 8-13 of the present specification. These test results establish that the composition of the present invention exhibits significant, unexpected and advantageously improved storage stability properties without requiring complicated techniques or the presence of one or more preservatives. In this regard, note that Example 1 at pages 8-9 of the present application establishes that vinflunine ditartrate is unexpectedly and advantageously more stable in the form of an aqueous solution according to the present invention, as compared to the "pulverulent" form. Example 2 establishes that the aqueous solution according to the present invention ("unbuffered") exhibited unexpected, advantageously improved stability over several formulations containing different buffers at different pH levels. All of the above-noted references cited in the above Office Action fail to disclose or reasonably suggest that these improved stability properties can be obtained by the aqueous formulation of the present invention.

5. The above-noted advantageous properties exhibited by the aqueous formulation according to the present invention were not conventionally recognized. This is evidenced by the presence of pH buffers and sugar derivatives such as mannitol which are present in the commercialized formulations for vincristine sulfate and vindesine sulfate injection formulations as evidenced by enclosed Exhibit A (Product label from http://www.accessdata.fda.gov/scripts/cder/onctools/labels.cfm?GN=vincristine) and Exhibit B (Eldisine®Injection from RxMed: Pharmaceutical information-Eldisine www.rxmed-com/b.main/b2.pharmaceutical/b2.1.monographs/...), respectively.

Significant Distinctions Between Vinflunine and Vinorelbine

6. As disclosed in Duflos '377, vinflunine is structurally related to vinorelbine, but differs in structure since it includes two fluoro substituents and a saturated bond in one of the heterocyclic rings, such that vinflunine is alternatively named as: 20',20'-difluoro-3',4'-dihydrovinorelbine. Even though vinflunine and vinorelbine may have similar therapeutic properties, these compounds exhibit significantly different physico-chemical properties in at least three areas when in the form of a powder or in the form of an aqueous solution.

7. First, there are significant differences in water solubility: vinorelbine tartrate has a solubility higher than 1000 mg/ml whereas vinflunine tartrate has a solubility equal to only 290 mg/ml.

8. Second, there are significantly different properties exhibited by each in the form of a powder after 6 months of storage at 5°C and 25°C: vinorelbine tartrate degrades such that the major impurity is due to the oxidation of the alcohol group in the vindoline structure, whereas in contrast, vinflunine ditartrate degrades such that the major impurity is 23-0 dimethylvinflunine which is due to the hydrolysis of the ester group of the vindoline structure. Therefore, vinorelbine tartrate and vinflunine ditartrate generate very different major impurities. This is evidenced by enclosed Exhibits C-1 and C-2 which show that vinorelbine tartrate generates the

impurity "S/D6" at 5°C and 25°C over time. Exhibit C-1 describes the impurity "S/D6" and corresponds to a portion of the documents submitted by the Assignee to appropriate regulatory authorities in order to obtain marketing authorization for the product described in the above-identified application. Exhibit C-2 includes two graphs showing the S/D6 content changes at "ambient" temperature (i.e. 25°C) and at "fridge" temperature (i.e. 5 °C). Labels "521", "522" and "524 correspond to different batches which were tested.

9. Third, the process for manufacturing vinflunine is totally different from the process for manufacturing vinorelbine. It is a more complex process since it requires a super acid medium. The differences between these two synthetic routes are illustrated in the enclosed Exhibit D.

10. Fourth, vinorelbine exhibits fungicidal activity after up to 28 days of contact with mold spores, with a slight fungicidal activity after 24 hours of contact. In contrast, vinflunine exhibits no fungicidal activity.

11. Consequently, several significant properties differ between these two compounds, such that one skilled in the art would not conclude it would be predictable to employ one compound in place of another and expect the same physico-chemical properties to be exhibited together with any improved storage stability properties.

12. Vinflunine generally appears to be less stable than vinorelbine since it has a lower solubility. Vinflunine degrades to form a major impurity significantly different from vinorelbine and does not exhibit fungicidal activity as does vinorelbine. Therefore, the behavior and stability of vinflunine in an aqueous solution can not be predicted based on the different physico-chemical properties exhibited by vinorelbine.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

June 26, 2009
Date

Eric Leverd

Enclosures: Curriculum Vitae
Exhibits A, B, C-1, C-2 and D